

## 7<sup>th</sup> International Syncope training Event September 13<sup>th</sup> & 14<sup>th</sup> 2018

### The ISSUE Studies



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In the late-1990s, the study of syncope was rendered easier and much more efficient by the availability of ILRs as described earlier. A number of studies supportive of the value of ILRs in this setting emanated from Italian investigators, primarily led by Michele Brignole (Lavagna).<sup>125,126</sup> The so-called ISSUE studies have helped to define the causes of syncope in a variety of clinical settings (i.e., isolated forms, syncope in the setting of known conduction system disease, etc.), and have also focused on the role of pacing in various types of neurally mediated syncope disease.

*In Cardiac Electrophysiology Methods and Models*  
Editors: Daniel C. Sigg, Paul A. Iaizzo, Yong-Fu Xiao, Bin He  
Springer 2010

**I**nternational (Italy & Spain)  
**S**tudy of  
**S**yncope of  
**U**ncertain  
**E**tiology

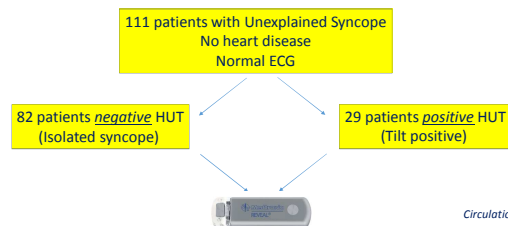
ISSUE

### ISSUE study Pre-defined inclusion categories

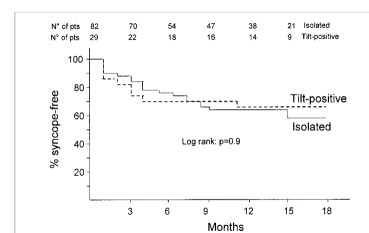
- Isolated syncope (true SUO)
- Tilt-induced syncope (suspected asystolic syncope)
- Structural heart disease: BBB, EP- (suspected intermittent AVB)
- Structural heart disease: NSVT, EP- (suspected VT/VF)
- Severe systolic dysfunction (suspected VT/VF)

### Mechanism of Syncope in Patients With Isolated Syncope and in Patients With Tilt-Positive Syncope

Angel Moya, Michele Brignole, Carlo Menozzi, Roberto Garcia-Civera, Stefano Tognarini, Luis Mont, Gianluca Botto, Franco Giada, Daniele Comacchia and on behalf of the International Study on Syncope of Uncertain Etiology (ISSUE) Investigators



Circulation 2001



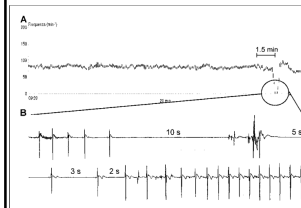
Moya et al., Circulation 2001

## Primary endpoint

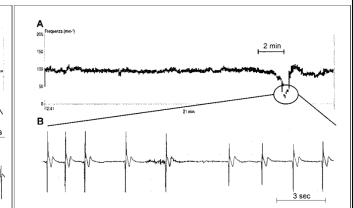
	Isolated (n=82)	Tilt-Positive (n=29)
Mean follow-up duration	9±5	10±5
Documented syncope, n (%)	24 (29)	8 (28)
Median time to first syncope, d (range)	105 (47–226)	59 (22–98)
<b>Findings at the time of syncope</b>		
Asystolic pause(s)	11 (46)	5 (62)
Maximum pause duration, s (range)	15±6 (6–24)	17±9 (3–21)
Asystole type: sinus arrest/AV block, n	9/2	5/0
Bradycardia <40 bpm, n (%)	2 (8)	1 (12)
Normal sinus rhythm, n (%)	9 (37)*	2 (25)
Sinus tachycardia, n (%)	1 (4)	0
Atrial tachycardia, n (%)	1 (4)	0

Moya et al., Circulation 2001

## Isolated syncope



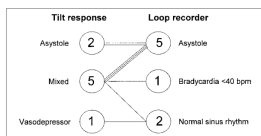
## Tilt positive



Moya et al., Circulation 2001

HUT has a low sensitivity and does not predict the type of spontaneous syncope

Presyncope is not syncope!



<b>Presyncope</b>		
Total patients with presyncope	19 (23)	7 (24)
Total number of presyncope episodes	24	14
Documented presyncope episodes	20	13
Relative bradycardia	4 (20)	2 (15)
Normal sinus rhythm	8 (40)	6 (46)
Paroxysmal supraventricular tachycardia	4 (20)	5 (38)
Sinus tachycardia	4 (20)	0 (0)

An excellent reproducibility of responses was observed when multiple syncopal or presyncopal episodes were documented in the same patient. This finding has a potential impact on therapy.

Moya et al., Circulation 2001

## ISSUE

## Conclusions

Circulation 2001;104:1261

In patients with isolated syncope:

the most frequent finding is an asystole secondary to progressive sinus bradycardia, suggesting a neuromediated origin

In patients with positive tilt test:

- similar results to isolated syncope, suggesting similar etiologies
- asystolic syncope also recorded when tilt testing was vasodepressor or mixed
- spontaneous syncope more frequently asystolic than expected

## Proposed electrocardiographic classification of spontaneous syncope documented by an implantable loop recorder

Europace 2005

Michele Brignole<sup>1,2</sup>, Angel Moya<sup>3</sup>, Carlo Menozzi<sup>4</sup>, Roberto Garcia-Civera<sup>5</sup>, Richard Sutton<sup>6</sup>

Type	ECG classification	Suggested pathophysiology
<b>Type 1. Asystole</b>	Type 1A. Sinus arrest	Probably reflex
	Type 1B. Sinus bradycardia plus AV block	Probably reflex
	Type 1C. Sudden onset AV block	Probably intrinsic or idiopathic ("low adenosine")
<b>Type 2. Bradycardia</b>	Decrease in HR >30% or <40 b.p.m. for >10 seconds	Probably reflex
<b>Type 3. No or slight rhythm variations</b>	Variations in HR <30% and HR >40 b.p.m	Uncertain
<b>Type 4. Tachycardia</b>	Type 4A. Progressive sinus tachycardia	Uncertain
	Type 4B. Atrial fibrillation	Cardiac arrhythmia
	Type 4C. SVT (except sinus)	Cardiac arrhythmia
	Type 4D. Ventricular tachycardia	Cardiac arrhythmia

www.escardio.org/guidelines

2018 ESC Guidelines on Syncope – Michele Brignole & Angel Moya  
EHJ Doc 10.1093/eurheartj/ehy037

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52 patients with Unexplained Syncope  
BBB  
Negative EEP

Bundle branch block type, n (%)	
Right plus right axis deviation	22 (42)
Right, no axis deviation	9 (17)
Left	20 (38)
Intraventricular conduction defect	1 (2)



Circulation 2001

## Mechanism of syncope in pts with BBB and negative EPS

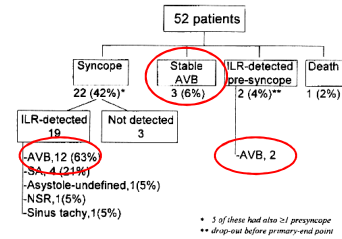
- N = 52 pts with documented syncope
- Negative criteria for syncope following
  - CSRT
  - HV  $\geq 7$  ms
  - Rapid atrial pacing  $\geq 150$  mg/kg
  - Sustained monomorphic VT
  - Rapid SVT



rapid atrial  
Ajmaline 1

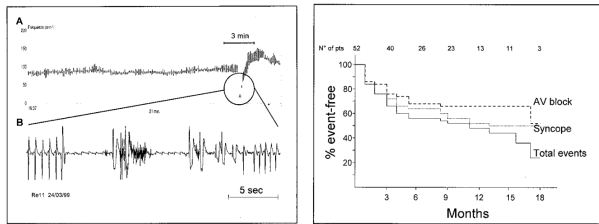
Brignole et al. Circulation 2001

## Mechanism of syncope in pts with BBB and negative EPS



Brignole et al. Circulation 2001

## Mechanism of syncope in pts with BBB and negative EPS



Brignole et al. Circulation 2001

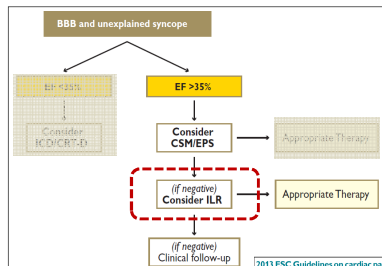
## Mechanism of syncope in pts with BBB and negative EPS

- 33% (17/52) of the pts had documented AVB during FU
- Only 6% of the pts have progression to permanent AVB
- No predictive factor but:
  - isolated RBB
  - a history of syncope  $> 2$  y.
- low risk of AVB

Brignole et al. Circulation 2001

## Unexplained syncope and BBB

Patients with BBB

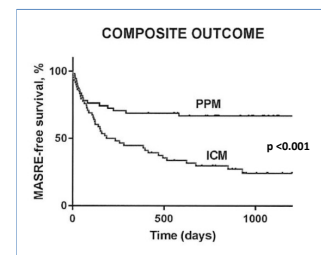


ESC Congress  
Munich 2018

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Brignole et al.

## A PPM for every patient with BBB and negative investigations?

- Syncope,
- Death,
- PPM complication,
- Symptomatic or asymptomatic bradycardia



ESC Congress  
Munich 2018

from Sheldon B et al., HRS meeting, Boston 2018



## ISSUE 2

### International Study on Syncope of Uncertain Etiology 2

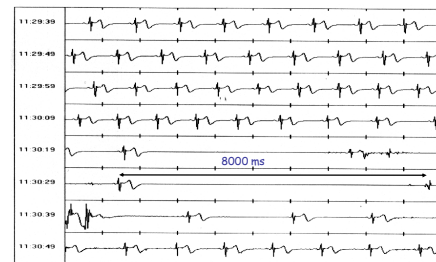
The management of patients with suspected or certain neurally-mediated syncope after the initial evaluation



Endorsed by the Working Group of Pacing of the European Society of Cardiology

With the organisational support of Medtronic Inc.

Spontaneous VVS : No prodrome → Trauma



### Pacing for VVS – « Initial » randomized studies

		Study Design*				TIS Table Criteria at Entry (% cardio-syncope)		Follow-up duration (months)	Randomized Patients		Age (mean, yrs)		
Total	Reference	Year	Allocation Concealment	Blinding	Personnel	Patients			n	Control	n		
Adams et al	7	1988	Unspecified	No	No	No	Positive T1T with loss of consciousness after falling medical therapy (2005)	17.3	300-400	12	300-400 PPM	6	61.1
Flammang	8	1989	Unspecified	No	No	No	Not performed (2005)	42	300	30	300-400	30	72.3
VPS	9	1989	Yes	No	No	No	Positive T1T with loss of consciousness after falling medical therapy (2005)	44	300-400	27	300-400 PPM	27	63.0
VASIS	10	2006	Yes	No	No	No	VASIS 1A or 2B (2005)	36	300-400	18	300-400 PPM	18	64.6
SYNCOPE	11	2005	Yes	No	No	No	Positive T1T with loss of consciousness after falling medical therapy (2005)	17.3	300-400	46	Altimeter	47	60.4
VPS II	12	2005	Yes	Yes	Yes	Yes	Positive T1T with loss of consciousness after falling medical therapy (2005)	44	300-400	48	300-400 PPM	52	68.2
Debraux	13	2003	Unspecified	No	Yes	Yes	Positive T1T with loss of consciousness after falling medical therapy (2005)	12	300-400 PPM	23	300 PPM	23	61.6
SYNCOPE**	14	2004	Yes	No	Yes	Yes	VASIS 1A or 2B (2005)	36	300-400 PPM	17	300-400 PPM	9	68.0
SYNCOPE II*	15	2004	Yes	Yes	Yes	Yes	Positive T1T with loss of consciousness after falling medical therapy (2005)	23.6	300-400 PPM	16	300-400 PPM	33	63.0
								6-62 months					
								218			212		

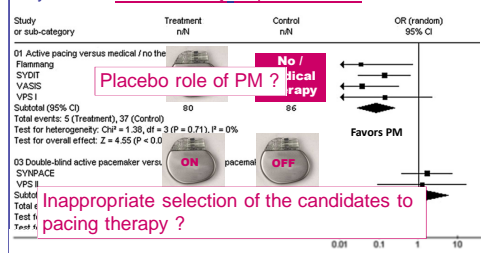
From Sud S et al. Am J Med 2007

### Active PM vs medical or no therapy



From Sud S et al. Am J Med 2007

### Only Pts with cardioinhibitory response to HUT



From Sud S et al. Am J Med 2007



## ISSUE 2

### International Study on Syncope of Uncertain Etiology 2

**Main objective:** To verify the value of ILR in assessing the mechanism of syncope and the efficacy of the ILR-guided therapy after syncope recurrence in patients with suspected or certain NMS after initial evaluation



## ISSUE 2 International Study on Syncope of Uncertain Etiology 2

### Inclusion criteria:

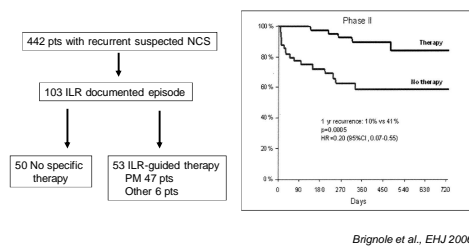
- Suspected or certain NMS, based on the Initial Evaluation of the ESC Guidelines on Syncope
- $\geq 3$  syncope episodes in the last 2 years
- Severe clinical presentation of syncope requiring treatment initiation in the judgement of the investigator
- Age  $>30$  years
- Patients have undergone carotid sinus massage, tilt testing and ILR implantation



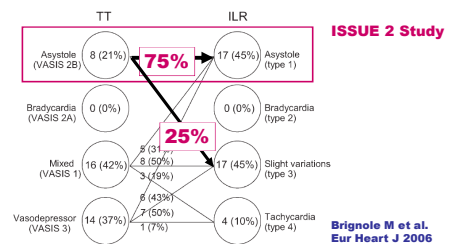
## ISSUE 2 International Study on Syncope of Uncertain Etiology 2

- Phase 1: ILR-based diagnosis
- Phase 2: ILR-guided therapy

### ILR-guided therapy and NCS ISSUE 2 study

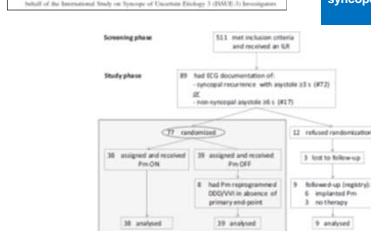


### Lack of correlation between the responses to tilt testing and the mechanism of spontaneous neurocardiogenic syncope



### Pacemaker Therapy in Patients With Neurally Mediated Syncope and Documented Asystole Third International Study on Syncope of Uncertain Etiology (ISSUE-3) A Randomized Trial

Michèle Brignole, MD, Carlo Menozzi, MD, Angel Moya, MD, Dietrich Anthelm, MD, Jean-Jacques Blanc, MD, Andrew D. Krause, MD, Walter Wieling, MD, Karel Benes, MD, René Claude Fréchet, MD, Vincent Basso, MD, Marco Tassinari, MD, Richard Sutton, DSc, on behalf of the International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators

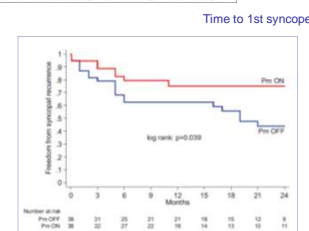


$\geq 40y$ ,  $\geq 3$  likely NM syncope in the last 2 years

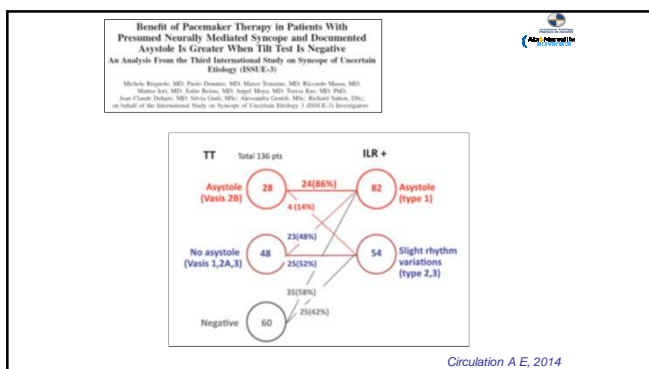
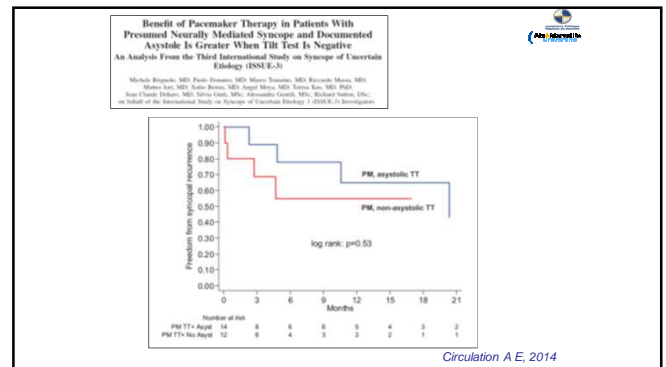
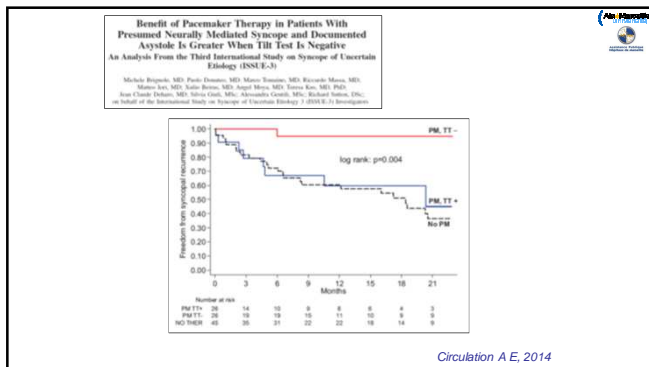
Circulation, 2012

### Pacemaker Therapy in Patients With Neurally Mediated Syncope and Documented Asystole Third International Study on Syncope of Uncertain Etiology (ISSUE-3) A Randomized Trial

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Circulation, 2012



ISSUE

**ISSUE 1 : what have we learnt ?**

- Bradycardia (and asystole) in "isolated" SUO and tilt-positive pts
- Sudden-onset paroxysmal AV block in BBB and negative EPS
- Heterogeneous mechanism in pts with structural heart disease and negative EPS. Ventricular tachyarrhythmia unlikely
- No syncope-related death
- Very low rate of syncope-related injury

ISSUE

**ISSUE 2-3 : what have we learnt ?**

- ILR guided therapy is effective in severe NMS
- The recurrence rate of syncope is not 0% (~20%), even in the ILR-guided therapy group
- A positive HUT is a predictor of syncope recurrence in paced patients (it denotes a vasodepressive susceptibility)